CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019675

Trade Name: ZANTAC SYRUP

Generic Name: RANITIDINE HCL SYRUP

Sponsor: GLAXO-WELLCOME

Approval Date: 12/30/88

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APPLICATION: 019675

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019675

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC - 4 1992

NDA:18-703(S-042)
19-675

Submission Date: May 24, 1991

Ranitidine HCl 150, and 300 mg tablets
Ranitidine HCl syrup.
Zantac[R] Tablets and Zantac Syrup.
Glaxo Inc.

Reviewer: Patrick J Marroum.

Type of submission: Supplement for approval for a higher dose to treat GERD.

Background:

Oral ranitidine (Zantac) at a dose of 150 mg bid is currently approved for relieving symptoms associated with gastroesophageal reflux disease. This supplemental application addresses the more severe forms of GERD. The sponsor is seeking approval for higher doses of ranitidine 150 mg qid for up to 12 weeks for both the approved tablets (150 mg) and the syrup.
Included in this submission are 2 multiple doses studies going up to 1200 mg per day and one drug interaction study with nifedipine at steady state with higher doses of ranitidine (300 mg bid).
The dose proportionality of ranitidine was already established up to 400 mg PO in the review of the original application (Biopharmaceutics review by Dr Huang dated August 11, 1982).
The pharmacodynamic portion of these studies are not going to be reviewed at this time. A more complete model of the pharmacodynamics and pharmacokinetics as well as the review of the pharmacodynamic results of these studies will be submitted at a later date.

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Study RAN 583	A study to compare the pharmacokinetics and pharmacodynamics of the interaction between multiple dose nifedipine (10 mg tid) with ranitidine (300 mg bid) and with cimetidine (800 mg mane)	10

Index: pem= post evening meal, mane= in the morning.

I-Summary of Bioavailability/Pharmacokinetics:

A- Dose and Dosage Form Proportionality:

The 2 studies in this submission investigated the pharmacokinetics of ranitidine following 300 mg bid, 600 mg qd, 300 mg qid and 1200 mg qd multiple dose regimens. These doses given over 7 days demonstrated that CMAX and AUC were proportionally related to dose. As expected with the 2 to 3 hour half-life of the drug, little accumulation was observed with dosing up to 300 mg qid.

II-DRUG INTERACTIONS:

1-Nifedipine:

Chronic administration of high doses of ranitidine (300 mg bid) did not have any effects on the pharmacokinetics and pharmacodynamics of nifedipine at steady state (10 mg tid).

III- Assay:

The sponsor of ranitidine. Unfortunately, no validation of either assays is presented in this submission.

Comments to be Sent to the Firm:

1- The sponsor is requested to submit validation data for both . Quality control samples showing the inter-assay and the intra-assay measure of variability should also be included.

2- In future drug interactions studies, it is recommended that both drugs, the drug under study as well as the interacting drug should be assayed.

Recommendation:

The sponsor's supplement of NDA 18-703 and 19-675 is acceptable for meeting the

biopharmaceutics requirements to support approval of the new dose of either 150 or 300 mg qid if the above Comment 1 is satisfactorily addressed by the firm.
Even though the sponsor did not validate the analytical assays used in this submission, the pharmacokinetic characteristics of ranitidine up to a single dose of 400 mg was adequately addressed in the original submission of this NDA.

Patrick J Marroum Ph.D 12/4/92

RD initialed by Parekh 12/4/92
FT initialed by Fleischer 12/4/92
cc: NDA 18703, 19675, HFD 180, HFD 426 (Marroum, Fleischer), Chron, Division, Drug, DI.

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24-hour intragastric acidity- a study to compare the effects of ranitidine 300 mg qid and ranitidine 1200 mg mane on days 1 and 8 of an eight day treatment period

Study: RAN-523. Volume: 84. Pages: 02-3-131

Investigators:

Clinical: Dr R E Pounder

Objectives:

To compare the effects (relative to placebo) of ranitidine 300 mg qid and ranitidine 1200 mg mane on days 1/2 and 7/8 of an eight day treatment period and to compare the difference between responses measured on days 1/2 and 7/8 with respect to:

1-24 hour intragastric acidity.
2-24 hour plasma gastrin concentrations.
3-pharmacokinetics of ranitidine.

Items 1 and 2 will be addressed in a subsequent review.

Formulation:

Ranitidine hydrochloride tablets (300 mg) pharmacy batch number 12/38 , expiration date February 1990.

Study Design:

24 healthy male volunteers between participated in this double-blind randomized comparison of 2 regimens of ranitidine and placebo. All subjects received placebo on the first study day which was carried out 14 days before study day 2. Subjects received treatment for 8 days and were studied on treatment day 1/2 and treatment day 7/8. Subjects 1 to 12 were randomized to receive either placebo or 300 mg ranitidine qid for 8 days. Subjects 13-24 were randomized to receive placebo or ranitidine 1200 mg mane for 8 days.

mls aliquots of gastric contents were aspirated hourly throughout the study and the pH of the aliquots measured immediately.

Plasma samples were collected hourly during the day and two hourly from 24:00 hrs until 8:00 AM for the measurement of plasma gastrin and plasma ranitidine.
All study medications (placebo or ranitidine) were administered immediately after meals. The meal compositions were not specified in the study.

Assay:

There was no validation data presented in this study.

Data Analysis:

The following variables were used to summarize the 24-hour period for pH and acidity.:

-The area under the acidity time curve
-the median pH.
-the number of hours that the pH was at or above pH 3.

The AUC for plasma gastrin concentration was calculated over the 24 hour period and over the daytime and night time periods. The % change in gastrin concentration during these periods was calculated with reference to the placebo day.
Correlation between gastrin and acidity was graphically examined.
The following pharmacokinetic parameters were summarized for each subject and treatment day:24-hour AUC, CMAX and the ratio of AUC on day 7/8 relative to day 1/2.
Correlation between AUC for ranitidine and AUC for acidity was examined.

Results:

1-Plasma Ranitidine:

The 24-hour median ranitidine profile for days 1/2 and days 7/8 is shown in Figure 1. Corresponding pharmacokinetic parameters were as follows:

	CMAX (ng/ml)		$AUC(ng/ml*hr)_{0-24h}$	
	Day 1	Day 7	Day 1	Day 7
300 mg qid	988.3 (282)	1021.4(383)	10952	12881
1200 mg mane	2843.2(610)	2480(488)	13161	13462

( ) = SD
Paired t-tests between day 1 and day 7 showed that there was no difference in any of the parameters when comparing the data for day 1/2 and day 7/8 (p value = 0.12). Plasma concentrations of ranitidine 300 mg qid were higher on day 7/8 than on day 1/2 as a consequence of detectable predose levels on day 7. The 24-hour AUC for ranitidine 300 mg qid was also comparable to the AUC for ranitidine 1200 mg mane.

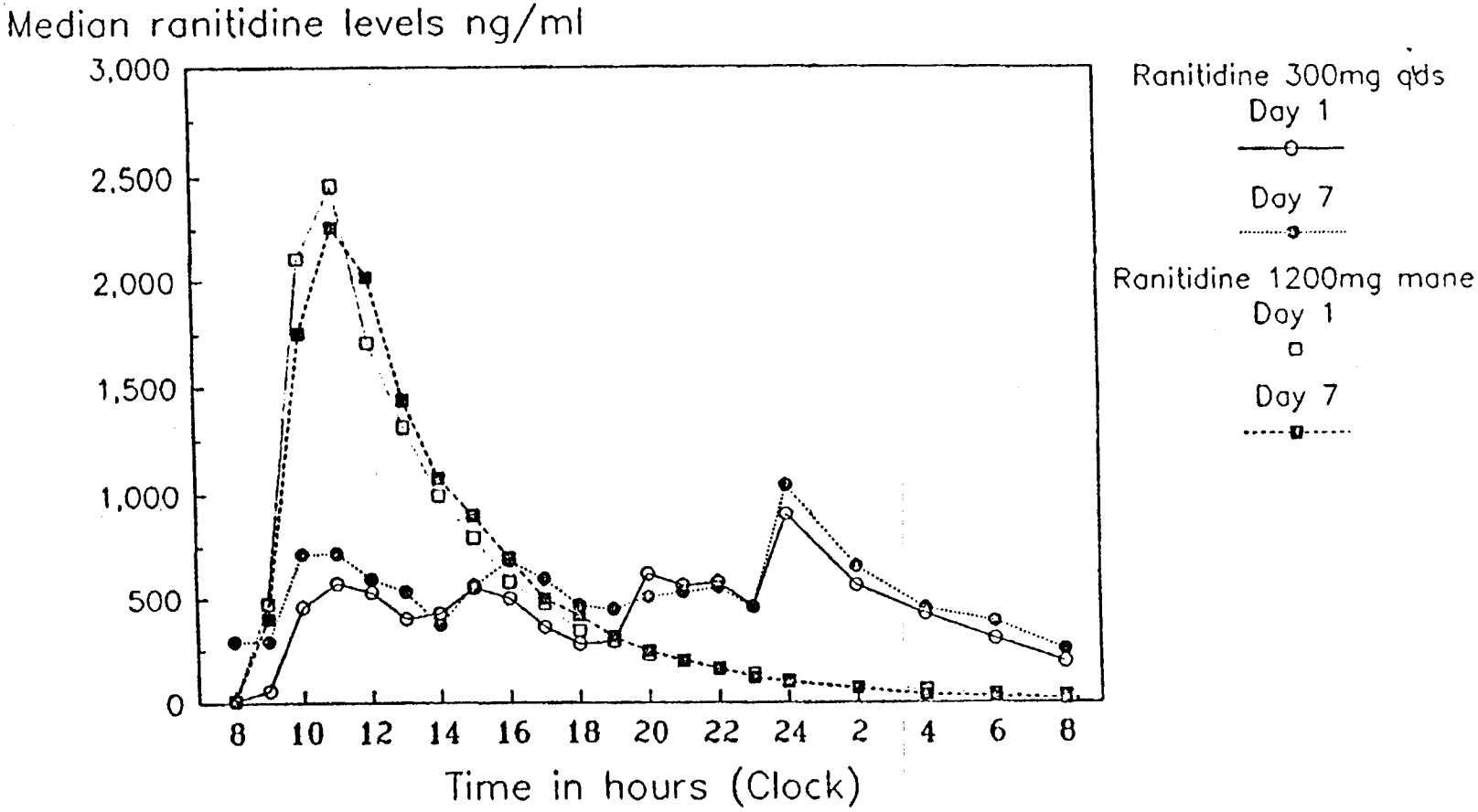
Figure 1

FIGURE 1

Fig 19:Median 24-hour plasma ranitidine profiles

16 healthy subjects

Ranitidine 300mg qds or 1200mg mane



ranitidine 300mg at 0830h, 1330h, 1830h, 2315h
ranitidine 1200mg at 0830h

24-hour intragastric acidity: A comparison of ranitidine 300 mg given after breakfast and post evening meal with 300 mg and 600 mg given post evening meal.

Study: RAN-1164 Volume: 84.2 Pages: 2-132 to 2-213

Investigators:

Clinical: Dr R.E. Pounder

Objectives:

The objectives of the study were to investigate the reduction in 24-hour intragastric acidity produced by three dosage regimens of ranitidine and to correlate this with plasma gastrin and plasma ranitidine concentration-time curves.

Formulation:

Ranitidine 300 mg tablets batch # 3/30A.

Study Design:

10 male subjects over the age of 18 completed this randomized (latin square), double blind placebo-controlled, crossover comparison of 3 dosage regimens of ranitidine. Each treatment was given for seven days and the subjects studied on day seven. There was a 1 week washout period between each treatment period.

aliquots of intragastric contents were aspirated hourly via a nasogastric tube and the pH of the aliquots measured immediately by means of a glass electrode and digital pH meter.

10 ml blood samples were taken hourly during the day and two hourly from midnight until 8 in the morning. Additional samples were taken at 30 and 75 minutes after the start of the three main meals.

Each subject received each of the following regimens for 7 days in a predetermined randomized order according to a repeated latin square:

a) Placebo.
b)Ranitidine 300 mg at 1930h after the evening meal.
c)Ranitidine 600 mg at 1930h after the evening meal.
d)Ranitidine 300 mg at 0930h after breakfast and ranitidine 300 mg at 1930h after the evening

meal.
Breakfast consisted of corn flakes in milk, one boiled egg, one slice of toast with butter, 50 ml of orange juice and 2 cups of tea. The supper was a fish and potato pie with peas, 180 ml of apple juice, 2 apple tarts and one cup of coffee. During the day, the subjects also had lunch and were allowed 3 snacks. Drug administration was always 15 minutes after the meals.

Assay:

No validation data was presented for both assays.

Data Analysis:

Data was analyzed exactly as described in the previous study.

Results:

1-Plasma ranitidine concentrations:

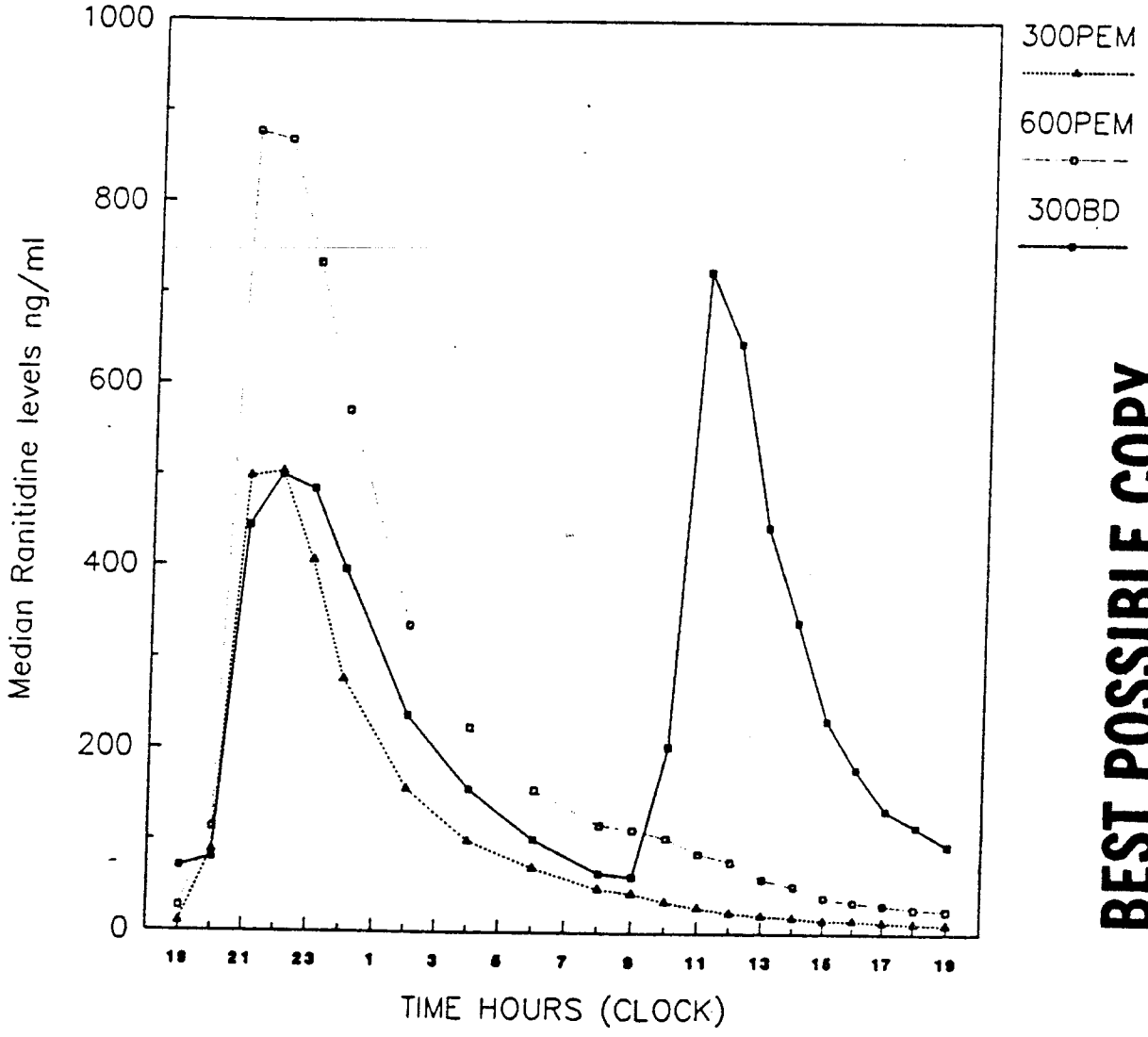
The median steady-state plasma ranitidine concentration-time profiles for all 3 treatments are shown in Figure 2. CMAX and AUC are summarized in the following table:

	CMAX (ng/ml)	AUC night 19-09	AUC day 9-19:00	AUC Total24hrs
300 mg pem	708(321)	2940 (777)	224 (101)	3164 (834)
600mg pem	1174(400)	5403 (859)	613 (248)	6016 (859)
300 mg bid breakfast	757(174)	3415 (880)	N/A	6544 (1288.4)
300 mg bid pem	695(308)	N/A	3129 (513)	N/A

( )= SD.
N/A= not applicable.

FIGURE 9

Median 24-hour plasma ranitidine profiles in 10 healthy subjects. Ranitidine was given at 1930h (post evening meal - pem) or at 0930h (after breakfast).



A study to compare the pharmacokinetics and pharmacodynamics of the interaction between multiple dose nifedipine (10 mg tid) with ranitidine (300 mg bid) and with cimetidine (800 mg mane).

Study: Ran 583. Volume: 84.2 Pages: 216-419.

Investigators: Dr Beverley L Holt

Objectives:

The study was undertaken to investigate the potential effects of high dose (300 mg bid) ranitidine on the steady state pharmacokinetics and pharmacodynamics of nifedipine as compared to the effects of a standard dosing regimen of cimetidine.

Formulation:

-10 mg nifedipine capsules (Adalat) batch # 602 expiration date 4-30-1991.
-ranitidine 300 mg tablets batch # 8/35 expiration date 4-30-1991.
-cimetidine 800 mg tablets batch # .0064 expiration date 4-30-1990.
-placebo batch # 88/084

Study Design:

18 non smoking male volunteers completed this randomized 3 way crossover design.
The 3 treatments were:

A- Ranitidine 300 mg bid + Nifedipine 10 mg tid for 4 days and the morning of the fifth day.

B- Placebo bid + Nifedipine 10 mg tid for 4 days and the morning of the fifth day.

C- Cimetidine 800 mg mane + Placebo nocte + Nifedipine 10 mg tid for 4 days and the morning of the fifth day.

10 ml blood samples were taken immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours post-dosing with nifedipine and ranitidine/cimetidine/placebo on day 5.

Assay:

Data Analysis:

Pharmacokinetic analysis was undertaken using the package. Assessment of the pharmacokinetics of nifedipine at steady state within an interdosing interval was undertaken using model independent means. AUC was calculated using the trapezoidal rule. In instances where experimental observations were available over the entire 8h interval, the additional area between the last experimentally determined concentration Ct and the 8h time point was calculated as:

$$AUC = Ct((1+e^{-k(8-t)})/2)*(8-t).$$

The apparent total clearance was calculated from D/AUC. CMAX and TMAX were observed values.
The apparent volume of distribution was calculated as V/F = Cl/F/K.

Results:

The mean plasma nifedipine concentration-time profiles are shown in Figure 5.
Following the administration of the final dose of nifedipine in the multiple dosing regimen, CMAX were achieved within The most important pharmacokinetic parameters are presented in Table 1. A summary of the most relevant pharmacodynamic parameters for nifedipine is presented in Table 2.

Chronic high doses of ranitidine was not found to produce any changes in the pharmacokinetics of nifedipine at steady state. Conversely, cimetidine produced large changes in the pharmacokinetics of nifedipine. CMAX increased by 128 %
Additionally, cimetidine was found to produce an approximate 50 % decrease in both the apparent volume of distribution (111.4 vs 51.7 l/hr) and the apparent volume of distribution (303 vs 164.7 l) resulting in a marginal change in the terminal half-life (2.02 +/- 0.89 vs 2.26 +/-0.51 hr).

Neither ranitidine nor cimetidine produced statistically significant changes in the pharmacological responses to nifedipine. However the lack of change in the pharmacological responses might be due to the insufficient power of the study to detect any significant pharmacodynamic differences due to the high variability of the pharmacodynamic responses measured.

The changes in the pharmacokinetic parameters of nifedipine upon coadministration with cimetidine is due to an inhibition by cimetidine of the enzymes responsible for first pass effect

and hepatic elimination resulting in an increased oral bioavailability of the calcium channel blocker.

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Figure 3 - Mean plasma nifedipine concentration-time profiles at steady-state following oral administration of 10mg tds to 18 young healthy male volunteers in the absence (PL) or presence of chronically administered ranitidine (RAN) or cimetidine (CIM)

Figure 3

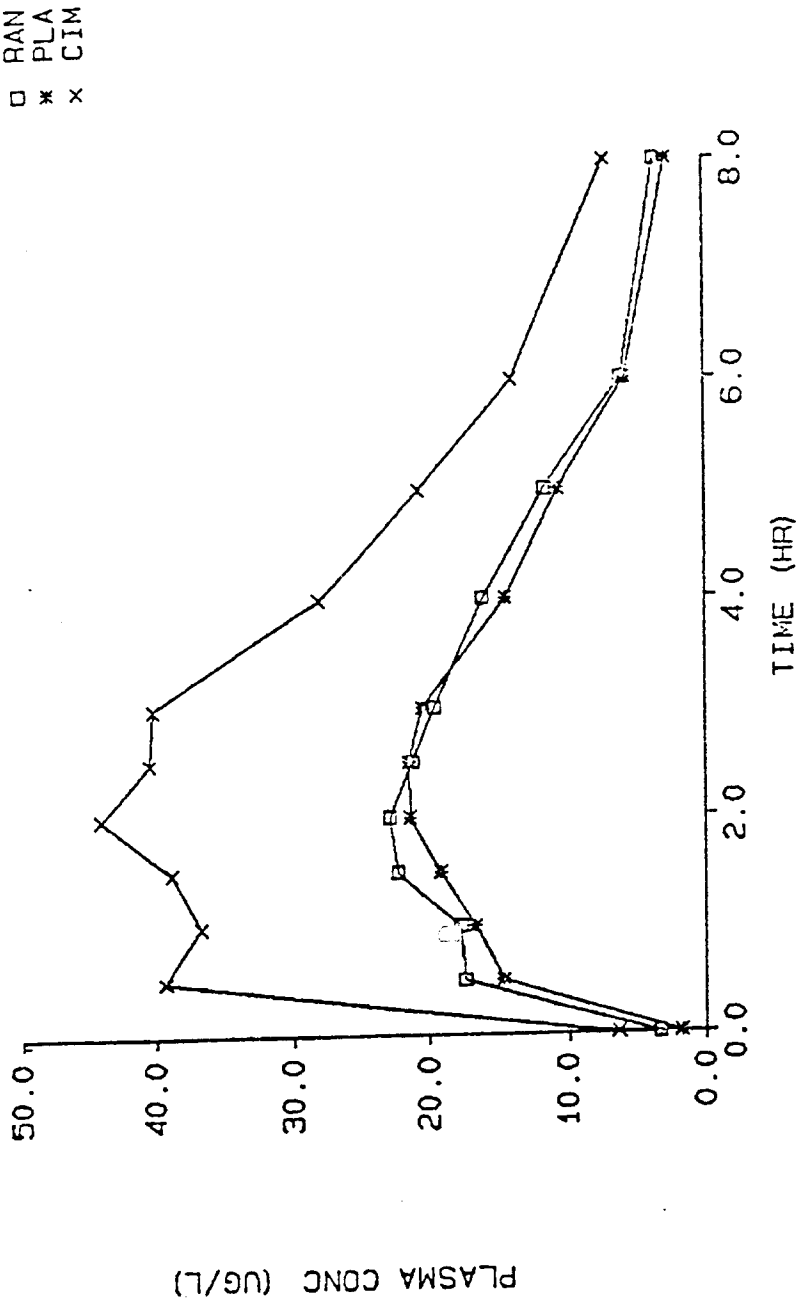

TABLE 2

11 - AVERAGE PARAMETERS USED TO QUANTIFY THE PHARMACOLOGICAL RESPONSE TO ...EDIPINE WITHIN AN INTER-DOSING INTERVAL AT STEADY STATE FOLLOWING THE ORAL ADMINISTRATION OF 10mg NIFEDIPINE (tds) TO 18 YOUNG HEALTHY MALE VOLUNTEERS IN THE ABSENCE (PL) AND PRESENCE OF CHRONIC CIMETIDINE (CIM; 800mg nane) AND RANITIDINE (RAN; 300mg bd)

Parameter	PL	RAN	CIM	Statistics
Weighted average pulse rate ($bt.min^{-1}$ ± sd)	64.32± 14.70	62.48± 5.95	62.04± 6.21	
Change in pulse rate ($bt.min^{-1}$ ± sd)	3.82 ± 4.68	1.59 ± 9.09	3.40 ± 4.17	Treatment - NS Sequence - p = 0.03
Weighted average systolic blood pressure (mmHg ± sd)	113.03 ± 9.91	113.83 ± 8.71	111.26 ± 7.65	
Change in systolic blood pressure (mmHg ± sd)	1.61 ± 8.58	3.51 ± 9.46	-0.96 ± 6.91	NS
Weighted average diastolic blood pressure (mmHg ± sd)	70.64 ± 8.11	71.80 ± 5.64	68.75 ± 5.65	
Change in diastolic blood pressure (mmHg ± sd)	-0.91 ± 6.73	-1.76 ± 7.26	-1.28 ± 6.94	NS
Weighted average P-R interval (ms ± sd)	161.49 ± 18.07	160.89 ± 17.14	160.31 ± 20.48	
Change in P-R interval (ms ± sd)	-6.96 ± 8.47	-5.94 ± 8.75	-6.14 ± 12.03	NS

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